Combined Deficiency of Coagulation Factors VIII and IX in an Ethiopian patient; a case report

Beniam Kassa[1], Binyam Birgane[1], Amha Gebremedhin[1], and Fissehatsion Woldegebriel[1]

[1]Addis Ababa University College of Health Sciences

February 28, 2025

Title :

Combined Deficiency of Coagulation Factors VIII and IX in an Ethiopian patient; a case report

Beniam Yohannes[1], Binyam Barega[1], Amha Gebremedhin[1], Fisihatsion Tadesse[1]

[1]Department of Internal Medicine, School of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

Correspondence: Beniam Yohannes, Department of Internal Medicine, School of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia. Tel +251964402936, Email byohannes631@gmail.com.

,

Introduction

Hemophilia is an X-linked recessive hemorrhagic disease due to mutations in the *F8* gene (hemophilia A or classic hemophilia) or *F9* gene (hemophilia B), leading to deficiency of factor VIII and IX respectively. The large size of the *F8* gene makes it more susceptible to mutation events than the smaller *F9* gene. Thus, Hemophilia A is more common than hemophilia B. Hemophilia affects more than 1.2 million individuals worldwide and occurs in all racial and ethnic groups. The majority of hemophilia patients give a positive family history with an x-linked inheritance pattern. However, a negative family history does not rule out hemophilia, because 20% to 30% of cases arise from a recent mutation, particularly in those with severe disease.[1,2]

The symptoms and signs of hemophilia A and B are indistinguishable. The severity and onset of bleeding depend on the severity of the disease. The Severity of the disease classified based on the factor activity as severe (<1%), moderate (between 1 and 5%), and mild (between 6 to 40%). Spontaneous bleeding is common in severe disease during early life and in moderate disease, bleeding usually occurs after minor traumas and surgical procedures. [3,4]

The presence of hemophilia A and B in one patient is extremely rare, and only a few case reports have been published. The clinical presentation of patients with coexisting hemophilia A and B was similar to the isolated hemophilia. Here, we present a 16-years-old male Ethiopian patient who initially presented with prolonged bleeding of 10 days duration after a circumcision procedure. To the best of our knowledge, this is the only case report from Africa.

Keywords : hemophilia A, hemophilia B

Case history and examination

A 16-year-old male patient presented with a complaint of unstoppable bleeding from a penile circumcision site of 10 days duration. He also gave history of recurrent easy bruising after minor trauma since childhood.

He is an only child in his family and has no remarkable family history of bleeding. Physical examination was remarkable for tachycardia (115 bpm), wide pulse pressure (BP: 125/60), pallor and active bleeding from the circumcision site on his penis.

Investigation and treatment

Laboratory examination revealed severe anemia (Hemoglobin of 5 mg/dl), prolonged activated Partial thromboplastin time (aPTT) of 120.8 seconds (laboratory range, 24.2 – 36.3 seconds), normal Prothrombin time (PT) of 11 seconds (laboratory range, 11 – 17.7), and INR of 1.18. After identification of a prolonged aPTT, a 1:1 mixing study was performed and aPTT was corrected. In such setting, though it's recommended to do assays for FVIII, FIX, FXI, and VWF, due to financial constraints only factor VIII level was determined and it came out to be 1.4%. With consideration of moderate Hemophilia A, he was started on recombinant factor VIII 750 IU BID and transfused 2 units of packed RBC. Subsequently, he showed some symptomatic improvement and the bleeding became intermittent but didn't stop completely. Repeat aPTT tests were prolonged, 96.2 seconds and 112.8 seconds. In addition, the hemoglobin started to drop again. The initial consideration was development of inhibitors but repeat FVIII level was.... With the above finding, the possibility of co-occurrence of hemophilia B with hemophilia A was suspected and Factor IX level was determined. The result showed a factor IX level of 5.5% (mild deficiency). The diagnosis of combined deficiency of Factor 8 and 9 was made and factor IX 1500 IU IV daily was added to the initial treatment, and the supportive management also continued

Outcome and follow-up

After administration of both factor VIII and IX, the bleeding has subsided and aPTT normalized. The patient was discharged and linked to follow-up clinic. Genetic study was planned but due to financial reason, it was not performed.

Discussion

The combined existence of hemophilia A and B is an extremely rare occurrence. It has been reported due to the inheritance of one variant from each parent or due to two variants from a single parent. Genetic studies from a few case reports showed denovo additional mutation of the genes with underlying congenital hemophilia A or B.[5,6]

Apart from inherited deficiency of factors, factor inhibition may also cause depletion of specific factors. Mixing study is used to determine the presence of any inhibitor in the blood of the patient. The correction of aPTT after 50:50 mix, easily rules out the possibility of inhibition.[7] After the possibility of factor inhibition is excluded, unreasonable bleeding with adequate replacement of factor products for the primary diagnosis was an entry point to suspect the possibility of this very rare incidence in case reports.

In a single case report from Lithuania, a patient who was known to have FIX deficiency since childhood, whereas hemophilia A was confirmed at the age of 42 years due to unexpected bleeding due to dental extraction despite adequate replacement with factor VIII concentrate. The deficiency was finally confirmed by genetic study showing point mutation in exon 2 for f9, whereas f8 gene analysis showed a point mutation in exon 4. The mother of the patient was heterozygous for f8 mutation, but not for f9. This suggests the denovo f9 mutation without any family history.[8]

Another case report from India, a 16-years-old male patient presented with knee hemarthrosis, with factor level assay showed both factor VIII and IX were below 1%. However, the detailed family history of the patient revealed no incidence of bleeding, which made it similar to the case we presented above. Genetic test was not done for this patient due to lack of the test in the center he was diagnosed. The patient was given both factor VIII and IX , after which the aPTT normalized.[9]

Patients with co-existing deficiency of both factor VIII and IX were also treated with factor replacement based on the severity of the particular factors. Because of the rare co-occurrence of hemophilia A and B, the prognosis and long-term treatment outcome of these subgroups of people is not known.

Conclusion

The presence of hemophilia A and B in one patient is an extremely rare event. The persistence of bleeding with adequate replacement of the factor should be the entry point of the overlap after excluding other possible causes of bleeding.

Data Sharing Statement

Laboratory investigations and patient physical findings used to support this study are included in the article.

Ethical Approval

The author's institution does not require ethical approval for the publication of a single case report.

Consent for Publication

The patient's family provided written informed consent for the publication of details including, history, physical findings, and laboratory reports. The written consent was witnessed and is held on file within our institution.

Acknowledgments

The authors thank the patient and his family for cooperating and being willing for the publication of the case.

Funding

No funding was used in this case report.

References

1. . Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, Germini F; Data and Demographics Committee of the World Federation of Hemophilia. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019 Oct 15;171(8):540-546. doi: 10.7326/M19-1208. Epub 2019 Sep 10. PMID: 31499529.

2. Shetty S, Ghosh K, Parekh S, Mohanty D. Combined factor VIII and IX deficiency in a family. Clin Lab Haematol. 2001 Jun;23(3):201-4. doi: 10.1046/j.1365-2257.2001.00381.x. PMID: 11553064.

3. Kulkarni R, Soucie JM, Lusher J, Presley R, Shapiro A, Gill J, Manco-Johnson M, Koerper M, Mathew P, Abshire T, Dimichele D, Hoots K, Janco R, Nugent D, Geraghty S, Evatt B; Haemophilia Treatment Center Network Investigators. Sites of initial bleeding episodes, mode of delivery and age of diagnosis in babies with haemophilia diagnosed before the age of 2 years: a report from The Centers for Disease Control and Prevention's (CDC) Universal Data Collection (UDC) project. Haemophilia. 2009 Nov;15(6):1281-90. doi: 10.1111/j.1365-2516.2009.02074.x. Epub 2009 Jul 22. PMID: 19637999.

4. Kulkarni R, Presley RJ, Lusher JM, Shapiro AD, Gill JC, Manco-Johnson M, Koerper MA, Abshire TC, DiMichele D, Hoots WK, Mathew P, Nugent DJ, Geraghty S, Evatt BL, Soucie JM. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. Haemophilia. 2017 Mar;23(2):207-214. doi: 10.1111/hae.13081. Epub 2016 Nov 4. PMID: 27813214; PMCID: PMC5354941.

5 .Prabhudesai A, Shanbhag S, Mirgal D, Kawankar N, Shetty S. A de novo factor VIII mutation in a haemophilia B family leading to combined deficiency of factor VIII and IX. Hemophilia. 2017;23(5):e477–79. [PubMed] [Google Scholar]

6. Carcao MD. The diagnosis and management of congenital hemophilia. Semin Thromb Hemost. 2012 Oct;38(7):727-34. doi: 10.1055/s-0032-1326786. Epub 2012 Sep 25. PMID: 23011791.

7. Lossing TS, Kasper CK, Feinstein DI. Detection of factor VIII inhibitors with the partial thromboplastin time. Blood. 1977 May;49(5):793-7. PMID: 856360.

8. Ivaškevičius V, Pezeshkpoor B, Biswas A, Goldmann G, Horneff S, Gimbutyte M, Malciute L, Jurgutis R, Oldenburg J. Combined coagulation factor VIII and factor IX deficiency (CDF8F9) in a patient from Lithuania. Hamostaseologie. 2016 Nov 8;36(Suppl. 2):S29-S33. PMID: 27824213.

9. Jamal I, Jeelani KA. Combined factor VIII and IX deficiency: An exceptional case. J Hematol Allied Sci. 2023;3:161-3. doi: 10.25259/JHAS_35_2023